Offer #2024-07734

PhD Position F/M Exploring the role of gene regulation in learning odors

Contract type : Fixed-term contract

Level of qualifications required : Graduate degree or equivalent

Fonction : PhD Position

About the research centre or Inria department

The Inria research centre in Lyon is the 9th Inria research centre, formally created in January 2022. It brings together approximately 300 people in 17 research teams and research support services.

Its staff are distributed in Villeurbanne, Lyon Gerland, and Saint-Etienne.

The Lyon centre is active in the fields of software, distributed and high-performance computing, embedded systems, quantum computing and privacy in the digital world, but also in digital health and computational biology.

Context

Within a long-term collaboration of the BEAGLE team with Dr. A. Fleischmann and Dr. R. Singh at Brown University (USA), you will investigate the gene regulatory processes involved in learning of odor responses in mice. Your goal will be to use both numerical (computational) modeling and bioinformatic data analysis to understand better how gene regulation impacts neuronal and glial behavior during learning in the olfactory system of mice, and vice versa, how learning an odor-response association has consequences for gene expression and gene regulation.

This is a three-year position for a PhD student. You will be advised by Anton Crombach (Centre Inria de Lyon), with expert input from Hugues Berry (Centre Inria de Lyon) and whilst working together with other members of the project. You will be located at Inria's La Doua site with opportunities to visit the collaborators at Brown University.

You will benefit from the expertise at Inria regarding bioinformatic data analysis and mathematical and computational modeling of biological systems; and you will profit from world-class knowledge at Brown University regarding neuro-biology and machine learning aspects of the project. Overall, the project will foster your career in terms of building up cutting-edge expertise on numerical simulation techniques, high-dimensional data analysis, network analysis, statistical and machine learning, and data visualization techniques – areas that are strongly demanded in academia and industry.

Assignment

This PhD project addresses a fundamental question in biology: how do we learn? As an example of learning, we study how mice learn to associate an odor with a positive or negative reward (water with sucrose or quinine, respectively). Specifically, we are interested in the impact of learning on gene expression in the mouse olfactory cortex. To this end, our collaborators at Brown University have generated a rich single-cell RNA sequencing dataset of olfactory cortex (piriform cortex) across a variety of conditions. Complementing the experimental work, our goal is to provide a formal framework to reason about the interplay between neuronal circuitry and the gene regulatory dynamics inside neurons and glial cells. This means we have two main objectives:

1. Create novel computational/mathematical models of olfactory neuronal circuits that interact with their associated gene regulatory networks in neurons and glia.

2. Perform bioinformatic data analysis of single-cell data to explore the role of glial cells, e.g. astrocytes, in learning, and how they interact with neurons in this process.

Regarding Objective 1, the computational modeling, the idea is to propose small "canonical" neuronal circuits present in olfactory cortex and to subject these circuits to different learning tasks, for instance to distinguish odor mixes. Learning is assumed to involve long-term changes of synaptic strength between neurons. The biological, and hence mathematical, details of how this is realized, however, remain an open question. Several phenomenological models have been proposed, but models with an explicit consideration of gene regulatory dynamics are rare (and tied to rather specific case studies). Given that nowadays scRNA-seq and related technologies provide us with the data at this level, our aim is to connect transcription and regulation of genes to the dynamics at synapses.

We will explore the regulation of synaptic strengths by means of evolutionary simulations. Using evolutionary approaches allows one to discover not only which mechanisms function correctly, but it also gives us an understanding of evolutionary properties, such as evolvability and robustness. Simulation results will then be used to formulate novel hypotheses that we can test given our collaborator's data, public datasets, and dedicated experiments.

Objective 2 will be done in close collaboration with the data analysis efforts by our collaborators at Brown University. They are focused on neurons that changed gene expression patterns due to learning. Complementing these efforts, we will focus on glial cells, exemplified here by astrocytes. Astrocytes are known to be involved in learning and our goal will be to describe, for olfactory cortex, how astrocytes change their expression dynamics. Next, by reaching out to local collaborators, Hugues Berry and Olivier Raineteau, we will investigate how interactions between neurons and astrocytes change due to learning. Insights from our data analysis efforts will allow us to go beyond mathematical models that are neuron-only and propose novel models that take into account the extensive cross-talk between neurons and glial cell types in the brain.

Main activities

Your main tasks are as follows:

- obtain a good overview of the relevant literature ("state of the art") regarding gene regulation, neuronal circuits, interactions between neurons and glial, single-cell data analysis, numerical simulations of evolution. You will be reading literature from both computational and experimental biology communities.
- formulate your approach(es) to address the challenges as described above in "Assignments". For computational modeling tasks, this requires designing and implementing mathematical models, and setting up evolutionary simulations. For bioinformatic data analysis, you will familiarize yourself with standard and advanced analysis software (Scanpy and tools from the *scverse* and/or Seurat and other R packages).
- conduct computational simulations and single-cell data analysis. Both simulation output and single-cell data are large, high-dimensional datasets. You will be using and adapting tools from statistics and machine learning to detect interesting patterns. It is likely that you will write custom code for specific tasks, for example when working with single-cell data, you will have to detect rare cell types, integrate temporal data, and compare multiple experimental conditions.
- communicate your results at conferences/workshops and via scientific articles. Effectively transmitting the core findings from your work is far from a trivial task, with a career-spanning learning curve.

Skills

The project requires skills in mathematics, computer science, and (neuro) biology. A successful candidate has experience in one or more of the following areas: dynamical systems theory, single-cell data analysis, statistics and machine learning, programming in Python/R and C/C++ (or similar, like Rust, Julia). Moreover, affinity with computational neuroscience is considered a real advantage. Good oral and written communication skills in English are essential.

Benefits package

- Subsidized meals
- Partial reimbursement of public transport costs
- Leave: 7 weeks of annual leave + 10 extra days off due to RTT (statutory reduction in working hours) + possibility of exceptional leave (sick children, moving home, etc.)
- Possibility of teleworking (90 days / year) and flexible organization of working hours (except for intership)
- Social, cultural and sports events and activities
- Access to vocational training
- Social security coverage under conditions

Remuneration

1st and 2nd year: 2100 euros gross salary /month

3rd year: 2190 euros gross salary / month

General Information

- **Theme/Domain :** Computational Biology
  Biologie et santé, Sciences de la vie et de la terre (BAP A)
- **Town/city :** Villeurbanne
- **Inria Center :** Centre Inria de Lyon
- **Starting date :** 2024-11-01
- **Duration of contract :** 3 years
- **Deadline to apply :** 2024-06-23

Contacts

- **Inria Team :** BEAGLE
- **PhD Supervisor :**
  Crombach Antonius / anton.crombach@inria.fr

About Inria

Inria is the French national research institute dedicated to digital science and technology. It employs 2,600 people. Its 200 agile project teams, generally run jointly with academic partners, include more than 3,500 scientists and engineers working to meet the challenges of digital technology, often at the interface with other disciplines. The Institute also employs numerous talents in over forty different professions. 900 research support staff contribute to the preparation and development of scientific and entrepreneurial projects that have a worldwide impact.

The keys to success

The applicant should have a strong basis in mathematics and biology (Master's degree or equivalent), ideally oriented toward computational biology and/or bioinformatic data analysis. An essential quality for this project is a keen interest to apply one's mathematical and computational skills to help answering biological questions. An interest in the evolution and functioning of gene regulation and neuronal circuits, plus a curiosity for single-cell technologies, is considered a real asset, as is wanting to communicate and collaborate with experimental biologists that study the mouse olfactory sensory system.

Warning : you must enter your e-mail address in order to save your application to Inria. Applications must be submitted online on the Inria website. Processing of applications sent from other channels is not guaranteed.

Instruction to apply

Applications must be submitted online via the Inria website. Processing of applications submitted via other channels is not guaranteed.

Defence Security :
This position is likely to be situated in a restricted area (ZRR), as defined in Decree No. 2011-1425 relating to the protection of national scientific and technical potential (PPST).Authorisation to enter an area is granted by the director of the unit, following a favourable Ministerial decision, as defined in the decree of 3 July 2012 relating to the PPST. An unfavourable Ministerial decision in respect of a position situated in a ZRR would result in the cancellation of the appointment.

Recruitment Policy :
As part of its diversity policy, all Inria positions are accessible to people with disabilities.